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K012077

510(k) Summary
Safety and Effectiveness
IMMULITE and IMMULITE 2000 Rubella IgM

This summary of safety and effectiveness information has been prepared in accordance with the requirements of SMDA 1990 and 21 CFR Part 807.92.

Name: **Address:**	Diagnostic Products Corporation 5700 West 96th Street Los Angeles, California 90045-5597
Telephone Number: **Facsimile Number:**	(310) 645-8200 (310) 645-9999
Contact Person:	Edward M. Levine, Ph.D. Director of Clinical Affairs
Date of Preparation:	January 8, 2002
Device Name: **Trade:**	IMMULITE® Rubella IgM IMMULITE® 2000 Rubella IgM
Catalog Number:	LKRM1(100 tests), LKRM2 (200 tests) L2KRM2 (200 tests), L2KHQ6 (600 tests)
Common:	Reagent system for the qualitative detection of IgM antibodies to rubella virus in human
Classification:	Class II device, 83-LFX (21CFR 866.3510)
Manufacturer:	Diagnostic Products Corporation 5700 West 96th Street Los Angeles, CA 90045 (The Quality System of Diagnostic Products Corporation is registered to ISO 9001:1994)
Establishment Registration Number	DPC's Registration Number 2017183
Substantially Equivalent Predicate Device:	Trinity Biotech™ CAPTIA Rubella-M (K885300)

Description of Devices: IMMULITE Rubella IgM and IMMULITE 2000 Rubella IgM are clinical devices for use with their respective IMMULITE and IMMULITE 2000 Automated Immunoassay Analyzers.

Intended Use of the Device:

IMMULITE® Rubella IgM – For *in vitro* diagnostic use with the IMMULITE Analyzer – for the qualitative detection of IgM antibodies to rubella virus in human serum or plasma (EDTA or heparinized), as an aid in the presumptive diagnosis of an acute or recent rubella infection, particularly in women of childbearing age.

IMMULITE 2000® Rubella IgM – For *in vitro* diagnostic use with the IMMULITE 2000 Analyzer – for the qualitative detection of IgM antibodies to rubella virus in human serum or plasma (EDTA or heparinized), as an aid in the presumptive diagnosis of an acute or recent rubella infection, particularly in women of childbearing age.

Performance Equivalence:

Diagnostic Products Corporation (DPC) asserts that IMMULITE Rubella IgM and IMMULITE 2000 Rubella IgM produce substantially equivalent results to other commercially marketed Rubella IgM assays, such as Trinity Biotech™ CAPTIA Rubella-M (K885300). The IMMULITE and IMMULITE 2000 Rubella IgM assays and Trinity Biotech CAPTIA Rubella-M are intended strictly for *in vitro* diagnostic use for the presumptive diagnosis of acute (current in CAPTIA Rubella M) or recent rubella infection.

Technology Comparison:

Provided below is a comparison of DPC's IMMULITE and IMMULITE 2000 Rubella IgM technology vs. the Trinity Biotech CAPTIA Rubella-M EIA technology.

IMMULITE Rubella IgM is a solid-phase, two-step chemiluminescent enzyme immunoassay. The solid phase, a polystyrene bead enclosed within an IMMULITE Test Unit, is coated with partially purified rubella antigen.

Prediluted patient sample (1-in-21 dilution) and a protein-based buffer are simultaneously introduced into the Test Unit, and incubated for approximately 30 minutes at 37°C with intermittent agitation. During this time, rubella-specific IgM in the sample binds to the rubella antigen-coated bead. Unbound serum is then removed by a centrifugal wash.

An alkaline phosphatase-labeled anti-human IgM antibody is introduced, and the Test Unit is incubated for approximately another 30-minute cycle. The unbound enzyme conjugate is removed by a centrifugal wash. Substrate is then added, and the Test Unit is incubated for a further 10 minutes.

The chemiluminescent substrate, a phosphate ester of adamantyl dioxetane, undergoes hydrolysis in the presence of alkaline phosphatase to yield an unstable intermediate. The continuous production of this intermediate results in the sustained emission of light, thus improving precision by providing a window for multiple readings. The bound complex -- and thus also the photon output, as measured by the luminometer -- is related to the presence of rubella IgM in the sample. A qualitative result is then obtained by comparing the patient result to an established Cutoff.

IMMULITE 2000 Rubella IgM is a solid-phase, two-step chemiluminescent enzyme immunoassay. The solid phase, a polystyrene bead added to an IMMULITE 2000 Reaction Tube, is coated with partially purified rubella antigen.

Prediluted patient sample (1-in-20 dilution) and a protein-based buffer are simultaneously introduced into the Reaction Tube, and incubated for approximately 30 minutes at 37°C with intermittent agitation. During this time, rubella-specific IgM in the sample binds to the rubella antigen-coated bead. Unbound serum is then removed by a centrifugal wash.

An alkaline phosphatase-labeled anti-human IgM antibody is introduced, and the Reaction Tube is incubated for approximately another 30-minute cycle. The unbound enzyme conjugate is removed by a centrifugal wash. Substrate is then added, and the Reaction Tube is incubated for a further 5 minutes.

The chemiluminescent substrate, a phosphate ester of adamantyl dioxetane, undergoes hydrolysis in the presence of alkaline phosphatase to yield an unstable intermediate. The continuous production of this intermediate results in the sustained emission of light, thus improving precision by providing a window for multiple readings. The bound complex -- and thus also the photon output, as measured by the luminometer -- is related to the presence of rubella IgM in the sample. A qualitative result is then obtained by comparing the patient result to an established Cutoff.

The **Trinity Biotech CAPTIA Rubella-M** assay utilizes the Enzyme Immunoassay (EIA) technique for the detection of antibody to rubella virus. Goat antibody against human IgM is immobilized on the inner surface of microtitration wells. When diluted patient serum is incubated in the well a proportion of the total IgM is "captured" by the surface-bound antibody. Unbound serum components are rinsed away. Surface-bound rubella IgM is then specifically detected by incubation with a tracer pre-complex of rubella antigen, biotinylated rubella monoclonal antibody and horseradish peroxidase-streptavidin. Unbound complex is rinsed away. Surface bound enzyme labeled complex is identified by reaction with a substrate and the chromogen tetramethylbenzidine. The intensity of the colored reaction product is directly proportional to the amount of rubella IgM initially "captured" on the solid phase.

Expected Values

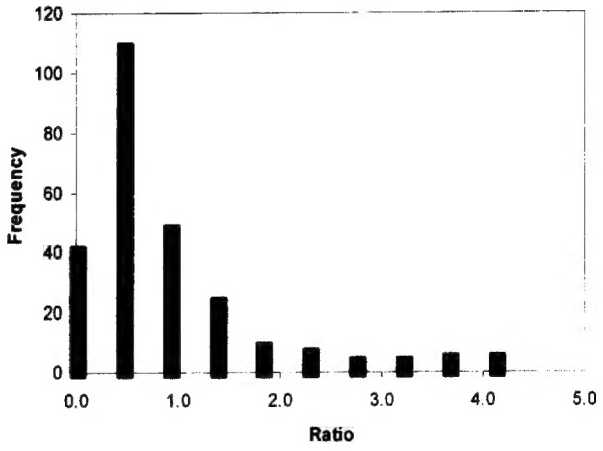
Individuals acutely infected with rubella virus will not exhibit detectable levels of IgM antibody in the early stages of infection. IgM antibodies to rubella virus are detected a few days after the onset of rash or vaccination. Peak IgM levels are reached in 3 to 6 weeks, then gradually decline over a period of months.

The prevalence of rubella infection can vary depending on a number of factors such as age, gender, vaccination history, geographic location, socio-economic status, race, type of test used, specimen collection and handling procedures and clinical and epidemiological history of individual patients.

IMMULITE Rubella IgM
Studies with presumed healthy, asymptomatic subjects and individuals suspected of acute rubella infection were conducted at two clinical sites in the southern and northeastern United States. The study in the southern United States consisted of 236 specimens from 92 pregnant women and 144 individuals with various conditions. IMMULITE Rubella IgM tests on these samples yielded the following results:

	Total	Positive		Negative		Indeterminate	
Subjects	n	n	%	n	%	n	%
Pregnant	92	5	6%	84	91%	3	3%
Various	144	45	31%	86	60%	13	9%
All	236	50	21%	170	72%	16	7%

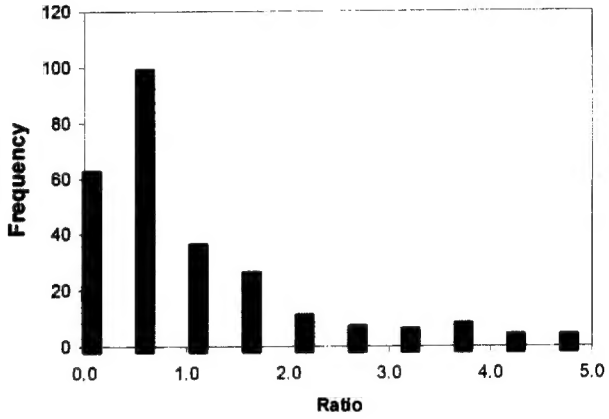
Observed signal/cutoff ratios for all samples



The study in the northeastern United States consisted of 233 specimens from 60 pregnant women and 173 individuals with various conditions. IMMULITE Rubella IgM tests on these samples yielded the following results:

	Total	Positive		Negative		Indeterminate	
Subjects	n	n	%	n	%	n	%
Pregnant	60	0	0%	60	100%	0	0%
Various	173	67	39%	97	56%	9	5%
All	233	67	29%	157	67%	9	4%

Observed signal/cutoff ratios for all samples

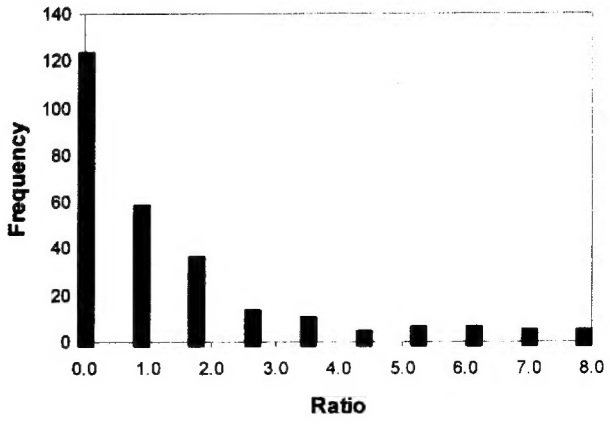


IMMULITE 2000 Rubella IgM

Studies with presumed healthy, asymptomatic subjects and individuals suspected of acute rubella infection were conducted at one clinical sites in the southern United States. The study consisted of 236 specimens from 92 pregnant women and 144 individuals with various conditions. IMMULITE 2000 Rubella IgM tests on these samples yielded the following results:

	Total	Positive		Negative		Indeterminate	
Subjects	n	n	%	n	%	n	%
Pregnant	92	13	14%	73	79%	6	7%
Various	144	61	42%	73	51%	10	7%
All	236	74	31%	146	62%	16	7%

Observed signal/cutoff ratios for all samples



Performance Characteristics

Clinical Performance

In a clinical study in the southern United States, a total of 236 frozen samples from apparently healthy male and female subjects, pregnant women and patients suspected of being rubella IgM positive were tested by IMMULITE Rubella IgM and by a commercially available enzyme immunoassay (Kit A - Trinity Biotech CAPTIA Rubella M). The IMMULITE Rubella IgM results were compared to the results of Kit A.

Comparison for all subjects

	IMMULITE Rubella IgM		
Kit A	Positive	Indeterm	Negative
Positive	45	12	7
Indeterm	3	4	8
Negative	2	0	155
Positive Agreement:	86.5% (45/52, 95% CI: 74.2% - 94.4%)		
Negative Agreement:	98.7% (155/157, 95% CI: 95.5% - 99.9%)		
Agreement:	95.7% (200/209, 95% CI: 92.0% - 98.0%)		

Comparison for pregnant subjects:

	IMMULITE Rubella IgM		
Kit A	Pos	Ind	Neg
Pos	3	2	1
Ind	1	1	6
Neg	1	0	77
Positive Agreement:	75.0% (3/4, 95% CI: 19.4% - 99.4%)		
Negative Agreement:	98.7% (77/78, 95% CI: 93.1% - 100%)		
Agreement:	97.6% (80/82, 95% CI: 91.5% - 99.7%)		

In another clinical study in the northeastern United States, a total of 233 frozen samples from apparently healthy male and female subjects, pregnant women and patients suspected of being rubella IgM positive were tested by IMMULITE Rubella IgM and Kit A. The IMMULITE Rubella IgM results were compared to the results of Kit A.

Comparison for all subjects

	IMMULITE Rubella IgM		
Kit A	Positive	Indeterm	Negative
Positive	66	6	8
Indeterm	0	1	13
Negative	1	2	136
Positive Agreement:	89.2% (66/74, 95% CI: 79.8% - 95.2%)		
Negative Agreement:	99.3% (136/137, 95% CI: 96.0% - 100%)		
Agreement:	95.7% (202/211, 95% CI: 92.1% - 98.0%)		

All 60 samples from pregnant subjects were negative by both IMMULITE Rubella IgM and Kit A, yielding a negative agreement of 100% (95% CI 94%–100%) for this group of subjects.

In the clinical study in the southern United States, the samples were also tested by IMMULITE 2000 rubella IgM, and Kit A. The IMMULITE 2000 Rubella IgM results were compared to the results of Kit A.

Comparison for all subjects

	IMMULITE 2000 Rubella IgM		
Kit A	Positive	Indeterm	Negative
Positive	59	5	0
Indeterm	8	2	5
Negative	7	9	141

Positive Agreement:	100%	(59/59, 95% CI: 93.9% - 100%)
Negative Agreement:	95.3%	(141/148, 95% CI: 90.5% - 98.1%)
Agreement:	96.6%	(200/207, 95% CI: 93.2% - 98.6%)

Comparison for pregnant subjects

	IMMULITE 2000 Rubella IgM		
Kit A	Pos	Indeterm	Neg
Pos	5	1	0
Ind	3	0	5
Neg	5	5	68

Positive Agreement:	100%	(5/5, 95% CI: 47.8% - 100%)
Negative Agreement:	93.2%	(68/73, 95% CI: 84.7% - 97.7%)
Agreement:	93.6%	(73/78, 95% CI: 85.7% - 97.7%)

In a study at DPC, IMMULITE 2000 Rubella IgM was compared to IMMULITE Rubella IgM on 223 samples:

	IMMULITE 2000 Rubella IgM		
IMMULITE	Positive	Indeterm	Negative
Positive	19	0	0
Indeterm	1	0	0
Negative	1	3	199

Positive Agreement:	100%	(19/19, 95% CI: 82.4% - 100%)
Negative Agreement:	99.5%	(199/200, 95% CI: 97.2% - 100%)
Agreement:	99.5%	(218/219, 95% CI: 97.5% - 100%)

Indeterminate results were excluded from calculations.

Performance Data

Precision (Serum): Precision studies for IMMULITE Rubella IgM assay were conducted at three different sites: in-house at DPC (Site 1) and at two sites in the southern and northeasten United States (Sites 2 and 3). At Site 1, samples were assayed in duplicate over the course of 20 days, two runs per day, for a total of 40 runs and 80 replicates. (See "Site 1" table). At Sites 2 and 3, samples were assayed in triplicate over the course of 5 days, one run per day, for a total of 5 runs and 15 replicates. (See "Site 2" and "Site 3" tables). The means, within-run and total CVs were calculated by the Analysis of Variance. Results are expressed as a signal-to-cutoff ratio. Precision statistics are summarized below.

IMMULITE Rubella IgM Precision – Serum (ratio):
Site 1

		Within-Run		Total	
	Mean	SD	CV	SD	CV
1	4.01	0.270	6.7%	0.348	8.7%
2	1.49	0.070	4.7%	0.098	6.5%
3	1.08	0.048	4.4%	0.075	7.0%
4	0.669	0.054	8.1%	0.064	9.6%
5	0.122*	—	—	—	—

* Consistently at a very low ratio

IMMULITE Rubella IgM Precision – Serum (ratio):
Site 2

		Within-Run		Total	
	Mean	SD	CV	SD	CV
1	3.20	0.207	6.5%	0.203	6.3%
2	1.43	0.062	4.3%	0.060	4.2%
3	1.06	0.049	4.6%	0.066	6.2%
4	0.690	0.080	11.6%	0.081	11.7%
5	0.229*	—	—	—	—

*Consistently at a very low ratio

IMMULITE Rubella IgM Precision – Serum (ratio):
Site 3

		Within-Run		Total	
	Mean	SD	CV	SD	CV
1	3.10	0.128	4.1%	0.116	3.7%
2	1.45	0.062	4.3%	0.059	4.1%
3	1.08	0.048	4.4%	0.056	5.2%
4	0.720	0.106	14.7%	0.111	15.4%
5	0.192*	—	—	—	—

* Consistently at a very low ratio

Precision (Serum): Precision studies for IMMULITE 2000 Rubella IgM assay were conducted at two different sites: in-house at DPC (Site 1) and in the southern United States (Site 2). At both sites, samples were assayed in triplicate over the course of 5 days, one run per day, for a total of 5 runs and 15 replicates. (See "Site 1" and "Site 2" tables). The means, within-run and total CVs were calculated by the Analysis of Variance. Results are expressed as a signal-to-cutoff ratio. Precision statistics are summarized below.

IMMULITE 2000 Rubella IgM Precision – Serum (ratio):
Site 1

		Within-Run		Total	
	Mean	SD	CV	SD	CV
1	5.40	0.450	8.3%	0.420	7.8%
2	1.81	0.116	6.4%	0.117	6.5%
3	1.24	0.105	8.5%	0.092	7.4%
4	0.810	0.122	15.1%	0.111	13.7%
5	0.166*	—	—	—	—

* Consistently at a very low ratio

IMMULITE 2000 Rubella IgM Precision – Serum (ratio):
Site 2

		Within-Run		Total	
	Mean	SD	CV	SD	CV
1	4.00	0.195	4.9%	0.32	8.0%
2	1.58	0.042	2.7%	0.108	6.8%
3	1.05	0.053	5.0%	0.065	6.2%
4	0.860	0.144	16.7%	0.174	20.2%
5	0.277*	—	—	—	—

*Consistently at a very low ratio

Precision (Plasma): Precision studies for IMMULITE Rubella IgM and IMMULITE 2000 Rubella IgM assays on plasma samples (EDTA and heparin) were conducted at DPC by testing samples in triplicate over the course of 3 days, two runs per day, for a total of 6 runs and 18 replicates. The means, within-run and total CVs were calculated by the Analysis of Variance. Results are expressed as a signal-to-cutoff ratio. Precision statistics are summarized below.

IMMULITE Rubella IgM Precision – EDTA (ratio):

		Within-Run		Total	
	Mean	SD	CV	SD	CV
1	0.128	0.044	34.4%	0.047	36.7%
2	0.78	0.057	7.3%	0.064	8.2%
3	1.12	0.062	5.5%	0.071	6.3%
4	1.62	0.099	6.1%	0.112	6.9%

IMMULITE 2000 Rubella IgM Precision – EDTA (ratio):

		Within-Run		Total	
	Mean	SD	CV	SD	CV
1	0.17	0.048	27.6%	0.045	25.9%
2	0.91	0.053	5.8%	0.048	5.3%
3	1.32	0.063	4.8%	0.063	4.8%
4	1.88	0.076	4.0%	0.083	4.4%

IMMULITE Rubella IgM Precision – Heparin (ratio):

		Within-Run		Total	
	Mean	SD	CV	SD	CV
1	0.42	0.114	27.1%	0.142	33.8%
2	0.91	0.137	15.1%	0.167	18.4%
3	1.21	0.115	9.5%	0.125	10.3%
4	1.62	0.2	12.3%	0.183	11.3%

IMMULITE 2000 Rubella IgM Precision – Heparin (ratio):

		Within-Run		Total	
	Mean	SD	CV	SD	CV
1	0.50	0.079	15.8%	0.084	16.8%
2	1.19	0.095	8.0%	0.088	7.4%
3	1.47	0.148	10.1%	0.130	8.8%
4	1.94	0.172	8.9%	0.148	7.6%

Crossreactivity: A study was conducted to evaluate whether the measurement of rubella IgM antibody is affected by closely related microorganisms. Ninety-one seronegative sera and one seropositive serum containing antibodies to Varicella Zoster Virus (n=3), Measles (n=10), Cytomegalovirus (CMV) (n=10), Herpes Simplex Virus (n=10), Toxoplasma (n=10), *mycloplasma pneumoniae* (n=10), Epstein-Barr Virus (n=10), Syphilis (n=10) and Parvovirus (n=10) and rheumatoid factor (n=9) were tested by IMMULITE and IMMULITE 2000 Rubella IgM. All 91 rubella IgM negative samples yielded negative results. A single rubella IgM positive serum with antibodies to measles virus was positive with the IMMULITE and IMMULITE 2000 Rubella IgM assay. This sample was further tested by a commercially available rubella IgM assay and yielded a positive result.

Interference: Conjugated or unconjugated bilirubin: no effect up to 20 mg/dL
Lipemia: no effect of triglycerides up to 3000 mg/dL
Hemoglobin: no effect up to 539 mg/dL

Anti-coagulants: Twenty-eight blood samples drawn into plain, heparinized and EDTA vacutainer tubes were assayed by the IMMULITE 2000 Rubella IgM assay. Results (in S/CO ratio) from the anticoagulant tubes were compared with those from the serum tubes in regression analyses:

Regressions:	Heparin = 0.94 × (Serum) + 0.04	r = 0.993
	EDTA = 0.95 × (Serum) + 0.01	r = 0.992
Means (S/CO ratio):	Serum = 0.85	
	Heparin = 0.83	
	EDTA= 0.82	

Gel Barrier: Twenty-eight blood samples drawn into plain and SST vacutainer tubes were assayed by the IMMULITE 2000 Rubella IgM assay. Results (in S/CO ratio) from the SST tubes were compared with those from the serum tubes in a regression analysis:

Regressions:	SST = 0.92 × (Serum) + 0.01	r = 0.993
Means (S/CO ratio):	Serum = 0.85	
	SST = 0.80	

Conclusion:

The data presented in this summary of safety and effectiveness is the data that the Food and Drug Administration used in granting DPC substantial equivalence for the IMMULITE Rubella IgM and IMMULITE 2000 Rubella IgM assays.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

JAN 1 0 2002

Edward M. Levine, Ph.D.
Director of Clinical Affairs
Diagnostic Products Corporation
5700 West 96th Street
Los Angeles, CA 90045-5597

Re: k012077
Trade/Device Name: IMMULITE® and IMMULITE® 2000 Rubella IgM
Regulation Number: 21 CFR 866.3510
Regulation Name: Rubella virus serological reagents
Regulatory Class: Class II
Product Code: LFX
Dated: November 30, 2001
Received: December 3, 2001

Dear Dr. Levine:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4588. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its internet address "http://www.fda.gov/cdrh/dsma/dsmamain.html".

Sincerely yours,

Steven Gutman

Steven I. Gutman, M.D., M.B.A.
Director
Division of Clinical Laboratory Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

510(k) Number: K012077

Device Name: **IMMULITE® Rubella IgM and IMMULITE® 2000 Rubella IgM**

Indications For Use:

IMMULITE® Rubella IgM – For *in vitro* diagnostic use with the IMMULITE Analyzer – for the qualitative detection of IgM antibodies to rubella virus in human serum or plasma (EDTA or heparinized), as an aid in the presumptive diagnosis of an acute or recent rubella infection, particularly in women of childbearing age.

IMMULITE 2000® Rubella IgM – For *in vitro* diagnostic use with the IMMULITE 2000 Analyzer – for the qualitative detection of IgM antibodies to rubella virus in human serum or plasma (EDTA or heparinized), as an aid in the presumptive diagnosis of an acute or recent rubella infection, particularly in women of childbearing age.

(PLEASE DO NOT WRITE BELOW THIS LINE - CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

Woody Dubois

(Division Sign-Off)
Division of Clinical Laboratory Devices
510(k) Number K012077

✓ Prescription Use (Per 21 CFR 801.109)

OR

Over-The-Counter Use

(Optional Format 1-2-96)